

P. INT COOPERATION TREA

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 October 2000 (11.10.00)	
International application No. PCT/EP00/01774	Applicant's or agent's file reference 9909388-Bzmi
International filing date (day/month/year) 02 March 2000 (02.03.00)	Priority date (day/month/year) 04 March 1999 (04.03.99)
Applicant KLUMPP, Susanne et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

07 September 2000 (07.09.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 9909388-Bzmi		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/01774	International filing date (day/month/year) 02/03/2000	Priority date (day/month/year) 04/03/1999
International Patent Classification (IPC) or national classification and IPC C12N15/55		
Applicant MERCK PATENT GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- ii ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 07/09/2000	Date of completion of this report 22.03.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/01774

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-16 as originally filed

Claims, No.:

1-11 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

Sequence listing part of the description, pages:

1-6 (numbered 17-22), as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☒ contained in the international application in written form.
 - ☒ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/01774

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
- ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-7, 10
	No:	Claims 8, 9, 11
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-11
Industrial applicability (IA)	Yes:	Claims 1-11
	No:	Claims

2. Citations and explanations
see separate sheet

**INTERNATIONAL ~~PRELIMINARY~~
EXAMINATION REPORT**

International application No. PCT/EP00/01774

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

II. Priority

Although the priority document discloses the same human gene and human and rabbit proteins as the filed application documents, the present claims are not entitled to priority. The present claims refer to a M.W. of 13-15 kDa instead of 13-14, use different sequences to define the peptides of the invention, introduce a new homology range in claim 6 and incorporate features from rat/mouse sequences first mentioned in filed document (i.e. X1 = R in claim 3). These features are not present or not used in their present context in the priority document.

V. Reasoned statement on Novelty, Inventive Step and Industrial Applicability

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

- Novelty (Art.33(2) PCT)

D1 discloses a human EST considered similar to Jan A. The EST comprises the whole of the reading frame of applicants histidine phosphatase (100% identity). Hence, D1 is cited against claims 8 and 9.

D6 discloses a collection of ESTs, one of which corresponds to applicants histidine phosphatase gene. DNA Seq.ID No.21 comprises the entire human gene (100% identity) and protein Seq.ID No.109 gives a 165aa protein which comprises the 125aa of applicants phosphatase plus 40aa upstream. It is suggested that the sequence is a homolog of the Drosophila Janus A gene and thus that it is a member of the family of non-receptor tyrosine kinases important in signal transduction. Because the putative protein of D6 is 165 rather than 125aa long, the complete protein does not fall within the claimed size-range (this renders most of the claims novel over D6. D6 does disclose antibodies to the protein (see claim 20), fragments thereof (claim 22), expression vectors, host cells, methods of protein production. Hence, D6 is cited against claims 8, 9 and 11.

- **Inventive Step (Art.33(3) PCT)**

D2 discloses an activity in rat liver (source of applicants protein) which phosphorylates His-75 of Histone H4. The activity is attributed to PP1 / PP2A_{1/2} histidine phosphatases. D3 characterizes PP1, PP2A and PP2C phosphatases purified from rabbit skeletal muscle. None of these enzymes appears to correspond to applicants enzyme since PP1 and PP2A are inhibited by okadaic acid and PP2C is inhibited by over 5mM Mg²⁺, which stimulates applicants enzyme (high activity at 10mM). D4 relates to a histidine phosphatase which is a dimer of 2 x 50 kDa and hence does not correspond to applicants protein. D4 employed a PHLase assay during purification.

The question of inventive step hinges very much on the definition of the closest prior art.

If one of the documents D2 to D4 which relate to other histidine phosphatases is taken as the closest prior art, then, using the problem-solution approach to inventive step, the problem addressed by the applicant is defined as the isolation of another mammalian histidine phosphatase. The solution is applicants histidine phosphatase. No teaching leads a skilled person from these documents to the isolation of the present enzyme which does not apparently belong to any of the families of phosphatases documented in said prior art.

However, the authorized authority is of the opinion that the technical field cannot be drawn so narrowly. Proteins involved in phosphorylation are now considered as instrumental in the study of signal transduction events involved in cancer. Taking this field, it is possible to use e.g. D1 (or D6 - possible in view of priority situation) as the closest prior art. The problem is defined as finding another protein involved in signal transduction. The skilled person sees from D1 or D6 that a sequence has been isolated which appears on the basis of sequence analogies to be a non-receptor tyrosine kinase of the Janus A type (i.e. a protein involved in signal transduction - as explicitly stated in e.g. D6). The difference between this sequence and the application is merely the specific activity (i.e. this is the only "solution"). In view of the potential commercial importance of the protein the skilled person presented with the sequence and putative function is

highly motivated to express it and test its function in a routine manner. As a result of this, the skilled person would inadvertently find the proteins activity (i.e. solve the technical problem). The fact that this activity is not as predicted (but falls within the same technical field) cannot render the gene or protein novel or inventive

Hence, inventive step is not acknowledged for the present claims.

- **Industrial Applicability (Art.33(4) PCT)**

The present claims appear to have industrial applicability.

VII. Certain Defects

The description seems to misrepresent and omit reference to the closest prior art documents. Documents D1 and D6 are not mentioned. Further, on p.4, l.23-26, it is stated that it has not been possible to identify histidine phosphatases in mammals. The disclosures of D2-D4, for example would appear to contradict this statement.

VIII. Certain observations

- **Clarity (Art.6 PCT)**

Claim 1 (and 6) can be understood as any polypeptide having the biological activity of the defined histidine phosphatase. If this interpretation is used then the claim is not novel over D2-D4, for example.

Claim 1 - terminology "high" (also in claim 6) specificity is unclear since high has no exact technical meaning. M.W. figures need to be accompanied by an indication of the method of determination. The chromatography steps outlined are so vague as to be virtually meaningless, since it is the conditions and method of activity screening that are critical.

Claim 6 - "homology" is not meaningful as opposed to e.g. "identity".

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 9909388-Bzmi	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/ 01774	International filing date (day/month/year) 02/03/2000	(Earliest) Priority Date (day/month/year) 04/03/1999
Applicant MERCK PATENT GMBH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

HISTIDIN PROTEIN-PHOSPHATASE

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/01774

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/55 C12N9/16 C07K16/40 A61K38/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HILLIER L. ET AL.: "zx64g11.r1 Soares_total_fetus_Nb2HF8_9w Homo sapiens cDNA clone" EMBL DATABASE ; ACCESSION NUMBER AA461149, 13 June 1997 (1997-06-13), XP002141076 the whole document	8,9
A	MATTHEWS HARRY R ET AL: "Protein histidine phosphatase activity in rat liver and spinach leaves." FEBS LETTERS, vol. 364, no. 1, 1995, pages 51-54, XP002141077 ISSN: 0014-5793 the whole document	1-11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 July 2000

Date of mailing of the international search report

19/07/2000

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/01774

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIM YOUNHEE ET AL: "Removal of phosphate from phosphohistidine in proteins." BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1268, no. 2, 1995, pages 221-228, XP000915034 ISSN: 0006-3002 the whole document ---	1-11
A	OHMORI HITOSHI ET AL: "3-Phosphohistidine/6-Phospholysine Phosphatase from Rat Brain as Acid Phosphatase." JOURNAL OF BIOCHEMISTRY (TOKYO), vol. 116, no. 2, 1994, pages 380-385, XP002141079 ISSN: 0021-924X abstract ---	1-11
A	OSTANIN, KIRILL ET AL: "Heterologous expression of human prostatic acid phosphatase and site-directed mutagenesis of the enzyme active site" J. BIOL. CHEM. (1994), 269(12), 8971-8 , XP002141080 page 8971 ---	1-11
P, X	DE 198 11 194 A (METAGEN GES FUER GENOMFORSCHUN) 16 September 1999 (1999-09-16) claim 22; figure SEQ.ID.109 -----	1-11

Information on patent family members

PS P 00/01774

Form PCT/ISA/210 (patent family annex) (July 1992)